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Distribution and Characterization of Motilin Receptors in the Cat

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DEPOORTERE, I., T. L. PEETERS AND G. VANTRAPPEN. *Distribution and characterization of motilin receptors in the cat.* PEPTIDES **14**(6) 1153–1157, 1993.—We demonstrate binding of [^{125}I][Nle^{13}-po]motilin to homogenates of cat gastric and small intestinal, but not to colonic smooth muscle tissue. The density was (B_{max} in fmol/mg protein): 0 (fundus); 12 ± 2 (corpus); 22 ± 3 (antrum); 55 ± 12 (duodenum); 44 ± 10 (jejunum); 17 ± 1 (ileum); 0 (colon). A significant ($p < 0.05$) difference was found between the dissociation constant for motilin in the stomach (pK_d = 8.84 ± 0.06) and in the small intestine (pK_d = 8.58 ± 0.08). The motilides erythromycin-A (EM-A), EM-523, and EM-A *N*-oxide displaced labeled [Nle^{13}-po]motilin bound to cat duodenal receptor with potencies (pK_d) of 5.47 ± 0.23, 7.60 ± 0.24, and < 4.3, respectively. Studies with [Leu^{13}-po]motilin fragments showed that the *N*-terminus of motilin interacts with the receptor. In the tissue bath, duodenal strips mounted in the longitudinal direction responded to motilin, EM-523, and EM-A (pEC_{50}: 8.29 ± 0.08; 7.12 ± 0.12; 5.99 ± 0.15). The compounds had a comparable intrinsic activity (83 ± 3%; 80 ± 5%; 82 ± 5% of the response to ACh), which was unaffected by atropine, TTX, hexamethonium, and zacopride but reduced by verapamil and calcium-free medium. Cat stomach and small intestine possess smooth muscle motilin receptors, which have comparable properties as those found in man and in rabbit.

Motilin receptors Binding sites Cat

BINDING sites for motilin, a 22 amino acid gastrointestinal peptide, were first demonstrated by Bormans et al. (3) in homogenates of rabbit antral smooth muscle tissue. Furthermore, it has been shown that in the rabbit, the receptor density decreases aborally along the small intestine, is absent in the caecum, and reappears in the colon, where it is almost four times the density found in the duodenum (7). The same regional distribution has been found in man (22), although motilin receptors have, up till now, not been demonstrated in the human colon. In dogs, motilin binding was undetectable in crude membrane preparations from antrum and duodenum (22).

In vitro studies have shown that motilin is able to induce contractions of smooth muscle strips from the antrum, duodenum, and colon of the rabbit and of the antrum and duodenum of man, by a direct action on smooth muscle cells (1,7,18,29). However, in the tissue bath, preparations from dog, guinea pig, or rat do not respond to motilin (15,28,29). Further studies have shown that in the rabbit motilin's action depends upon the influx of external Ca^{2+} (20) and that the peptide may release Ca^{2+} from intracellular stores (21) by stimulating the release of inositoltriphosphate (8).

In this study, we made a detailed exploration of the distribution and the binding characteristics of motilin receptors along the gastrointestinal tract of the cat. Simultaneously, the in vitro mechanism of action of motilin in the cat was investigated by measuring the in vitro response of duodenal strips in an organ bath.

In vivo studies have shown that erythromycin (EM) and its derivatives mimic the action of motilin in man (30) and in dog (14). In vitro studies have shown that in rabbit and in man, EM (23) and its derivatives (4,5) act on the motilin receptor. Their action involves, as for motilin, a direct effect upon smooth muscle tissue with both an influx of external Ca^{2+} and a release of Ca^{2+} from intracellular stores (24). Therefore, the in vitro effect of these compounds in the cat was studied as well.

METHOD

Reagents

The synthetic nor-leucine^{13} analogue of porcine motilin ([Nle^{13}-po]motilin) was purchased from Novabiochem (Läufelfingen, Switzerland). Erythromycin A (EM-A) and erythromycin A *N*-oxide (EM-A *N*-oxide) were a gift from Prof. J. Hoogmartens (Lab. of Pharmaceutical Chemistry, University of Leuven, Leuven, Belgium). EM-523 [de(*N*-methyl)-*N*-ethyl-8,9 anhydroerythromycin A 6,9-hemiacetal], developed by Dr. Omura of the Kitasato Institute (Tokyo, Japan), was a gift from Takeda Chemical Industries Ltd. (Osaka, Japan). The motilin fragments were a gift from Dr. A. Galdes (BOC Group, New Providence, NJ). Atropine sulfate, tetrodotoxin (TTX), verapamil hydrochloride, and hexamethonium chloride were purchased from Sigma (St. Louis, MO). Zacopride was a gift from Dr. C. Eeckhout (Kalichemie, Hanover, Germany).

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Binding Studies

Binding studies were carried out on homogenates prepared from cat stomach, small intestine, and colon. Cats of either sex were killed by injection of 2 ml Ketalar (5 mg/ml). The stomach, small intestine, or colon were rapidly removed and rinsed with 0.9% NaCl. The stomach was divided into three parts (fundus, corpus, and antrum); the small intestine was cut into three parts of approximately 30-cm length (duodenum, jejunum, and ileum). Smooth muscle tissue was freed from mucosa and submucosa, finely minced, and homogenized using a Potter S homogenizer (Braun, Melsungen, Germany) at 1500 rpm.

Binding of [^{125}I][Nle^{13}-po]motilin was studied in washed, 1000 $\times$ *g* fractions of the tissue homogenates as previously described (3). Briefly, membranes were incubated with [^{125}I][Nle^{13}-po]motilin (specific activity: $\pm$ 1500 cpm/fmol, final concentration 50 p*M*) in 50 m*M* Tris buffer (1.5% BSA, 10 m*M* $MgCl_2$, pH 8.0, total volume: 0.8 ml) for 60 min. The reaction was stopped by adding 3.2 ml of cold buffer, and membrane-bound motilin was separated by centrifugation at 1000 $\times$ *g*. All data were corrected for nonspecific binding determined after the addition of an excess of [Nle^{13}-po]motilin. Displacement curves were obtained by adding increasing amounts of [Nle^{13}-po]motilin, EM-A, EM-523, EM-A *N*-oxide, or motilin fragments to the incubation media, and the negative logarithm of the concentration displacing 50% of the label (pIC_{50}) was calculated by linear interpolation. The dissociation constant (K_d) and the maximal amount of binding sites (B_{max}) were calculated from displacement curves fitted by the nonlinear least-squares curve-fitting procedure of the SAS software program (SAS Institute Inc., Cary, NC, USA). In these calculations, it was assumed that labeled motilin has the same affinity as nonlabeled motilin for the receptor. Dissociation constants are always given as negative logarithms of the molar concentration to which they correspond (pK_d).

Contraction Studies

The biological activity of [Nle^{13}-po]motilin, EM-A, and its derivatives was tested in a tissue bath by measuring its contractile effect on strips of cat duodenum. A segment of the duodenum was removed and placed in oxygenated Hepes buffer (11.6 m*M* Hepes, 137 m*M* NaCl, 5.9 m*M* KCl, 2.5 m*M* $CaCl_2$, 1.2 m*M* $MgCl_2$, 11.5 m*M* glucose, pH 7.4) at room temperature. The mucosa and the submucosa were removed and the muscle segments were cut into strips measuring 1.5 $\times$ 15 mm. These strips were oriented in the longitudinal axis in a tissue bath, continuously gassed with 100% O_2, and thermostatted at 37°C. Cumulative concentration–response curves were established by adding increasing amounts of compound, and the negative logarithm of the concentration giving 50% of the maximum contractile response (pEC_{50}) was calculated. The response was always expressed relative to the maximum obtained with ACh (10^{-4} *M*). The effect of blocking agents (atropine, TTX, verapamil, hexamethonium, zacopride) was studied by incubating strips for 10 min, prior to a challenge with [Nle^{13}-po]motilin.

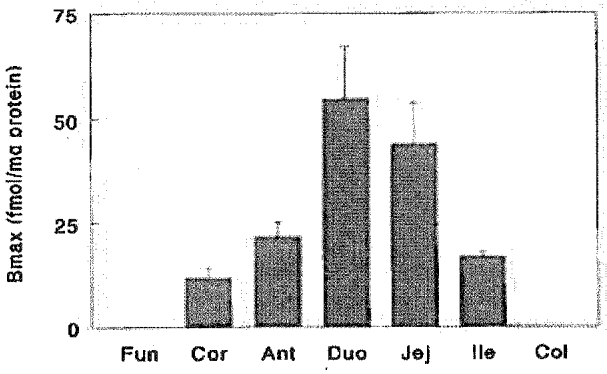

FIG. 1. Distribution of the motilin binding sites (B_{max} in fmol/mg protein) along the gastrointestinal tract of the cat. Binding experiments were performed with crude membrane preparations from fundus (Fun), corpus (Cor), antrum (Ant), duodenum (Duo), jejunum (Jej), ileum (Ile), and colon (Col).

TABLE 1

BINDING PARAMETERS DERIVED FROM DISPLACEMENT CURVES USING CRUDE MEMBRANE PREPARATIONS FROM DIFFERENT PARTS OF THE GASTROINTESTINAL TRACT OF THE CAT

	n	B_{max} (fmol/mg protein)	pK_d ($-\log K_d$)
Fundus	3	0	—
Corpus	2	11.9 $\pm$ 2.4	8.86 $\pm$ 0.06
Antrum	6	21.8 $\pm$ 3.4	8.83 $\pm$ 0.07
Duodenum	3	54.8 $\pm$ 12.4	8.52 $\pm$ 0.12*
Jejunum	4	44.1 $\pm$ 9.7	8.51 $\pm$ 0.18
Ileum	4	16.9 $\pm$ 1.3	8.70 $\pm$ 0.07
Colon	3	0	—

n = number of experiments; B_{max} and pK_d were derived from curve fittings by computer. The values shown are the mean $\pm$ SEM for the number of experiments as indicated.

* Indicates a significant difference compared to the value obtained for the antrum.

Data Analysis

Values are given as mean $\pm$ SEM. The pK_d values of the different regions were compared by analysis of variance (ANOVA) and were performed with the SAS software package. Specific comparisons were based upon *t*-tests, using the appropriate standard errors, as incorporated into the SAS software.

RESULTS

Binding Studies

In exploratory experiments with homogenates from cat antral smooth muscle tissue, specific motilin binding was easily demonstrated with our protocol established for rabbit tissue. Total binding was about 7% of the total amount of labeled [Nle^{13}-po]motilin added; the nonspecific binding was 1%. Receptor density and dissociation constant were then determined in different parts.

Figure 1 shows the distribution of motilin receptors along the gastrointestinal tract of the cat. The receptors are absent in the fundus, increase in density from the corpus (B_{max}: 11.9 $\pm$ 2.4 fmol/mg protein) to the duodenum (B_{max}: 54.8 $\pm$ 12.4 fmol/mg protein), and decrease towards the ileum (B_{max}: 16.9 $\pm$ 1.3 fmol/mg protein) to completely disappear in the colon. Table 1 recapitulates the B_{max} values along with the dissociation constants (pK_d) for motilin in the different regions. Although ANOVA did not reveal a significant difference of the pK_d in the different regions ($F = 1.61$, $p = 0.23$), specific comparisons between the

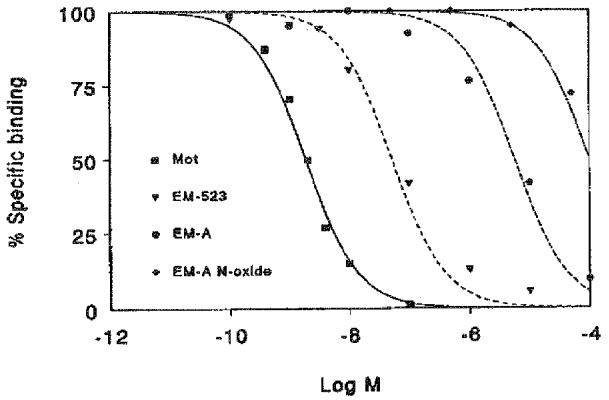

FIG. 2. Displacement of iodinated [Nle^{13}-po]motilin bound to a crude membrane preparation from cat duodenum by unlabeled [Nle^{13}-po]motilin, EM-523, EM-A, and EM-A *N*-oxide.

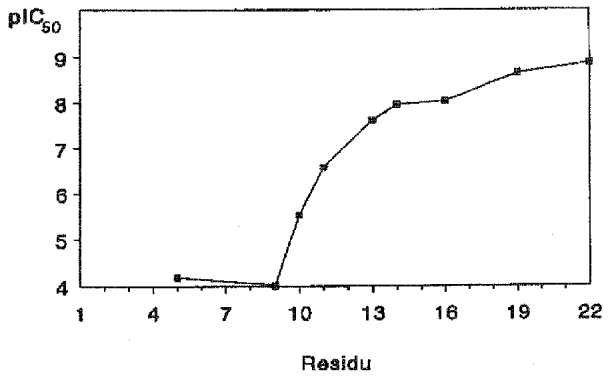

FIG. 3. pIC_{50} values as a function of chain length for [Leu^{13}-po]motilin fragments extended from their *N*-terminal end. The pIC_{50} values were derived from displacement curves on crude membrane preparations of cat antrum.

value of the antrum with those of the other regions revealed a significant difference in the duodenum ($p < 0.05$) and a nearly significant difference for the jejunum ($p = 0.058$). Also, a comparison between the combined values for the stomach and for the small intestine (overall means of 8.84 ± 0.06 and 8.58 ± 0.08, respectively) reached significance ($p < 0.05$).

The effect of EM-A and its derivatives on [^{125}I][Nle^{13}-po]motilin binding in the cat was also investigated. The displacement curves obtained by incubating duodenal smooth muscle homogenates with [^{125}I][Nle^{13}-po]motilin and increasing concentrations of [Nle^{13}-po]motilin, EM-523, EM-A, and EM-A *N*-oxide are depicted in Fig. 2. Mean values of the pK_d data are summarized in Table 2. The order of potency was: [Nle^{13}-po]motilin > EM-523 > EM-A > EM-A *N*-oxide.

Table 2 compares the pK_d values obtained in the antrum with those obtained in the duodenum. ANOVA revealed a highly significant difference between both tissues ($F = 30.6$, $p < 0.01$) and of course between the different compounds. For all compounds the pK_d was significantly higher in the antrum, but the difference depended upon the compound ($F = 4.29$, $p < 0.05$).

Several *N*-terminal [Leu^{13}-po]motilin fragments of increasing length were tested for their ability to displace [^{125}I][Nle^{13}-po]motilin bound to cat antral smooth muscle membranes. The results are shown in Fig. 3. The *N*-terminal fragments (1–5), (1–9), and (1–10) had limited potency (pIC_{50}: 4.19, 4.02, and 5.53, respectively). Further extending the molecule to the *C*-terminal end gradually increased the affinity of the fragments for binding to the motilin receptor. For fragment (1–16) the pIC_{50} value was 91% of the value obtained for the complete molecule. Comparable results were obtained with this fragment in rabbit (19) and in human tissue (unpublished), where it was respectively 94% and 87% of the value found for the (1–22) peptide.

TABLE 2

COMPARISON OF THE pK_d VALUES (MEAN ± SEM) OBTAINED FROM BINDING STUDIES ON MEMBRANE PREPARATIONS FROM ANTRUM AND DUODENUM

	Antrum	Duodenum
[Nle^{13}-po]Motilin	8.83 ± 0.07 [6]*	8.52 ± 0.12 [3]
EM-523	8.18 ± 0.25 [3]*	7.60 ± 0.24 [3]
EM-A	6.69 ± 0.09 [3]*	5.47 ± 0.23 [3]
EM-A *N*-oxide	Not tested	<4.3 [3]

Number of experiments in brackets.
* Significantly ($p < 0.05$) different from the values obtained in the duodenum.

Contraction Studies

Increasing doses of motilin, added in a cumulative manner to the tissue bath, induced stepwise increases in tonus of cat duodenal smooth muscle strips (Fig. 4). The pEC_{50} value calculated from this figure was 7.96 and the maximum response was 83% of the response to a supramaximal dose of ACh (10^{-4} *M*). Figure 5 summarizes the dose–response curves of motilin, EM-523, EM-A, and EM-A *N*-oxide. The pEC_{50} data derived from this graph were: 8.29 ± 0.08 (motilin); 7.12 ± 0.12 (EM-523); 5.99 ± 0.15 (EM-A). This is the same order of potency as obtained in the binding studies. No difference was found between

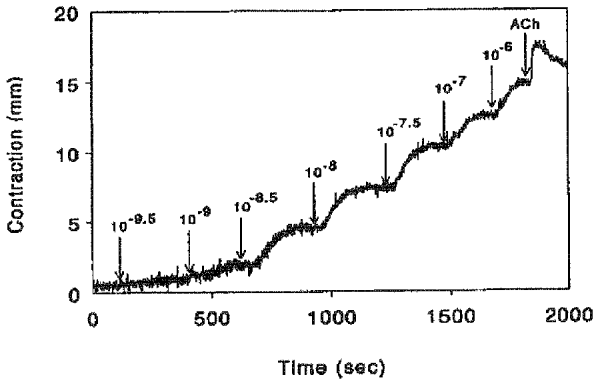

FIG. 4. Contractile response of a cat duodenal muscle strip to cumulative concentrations of [Nle^{13}-po]motilin. At the end of the dose–response curve a supramaximal dose of ACh (10^{-4} *M*) was given.

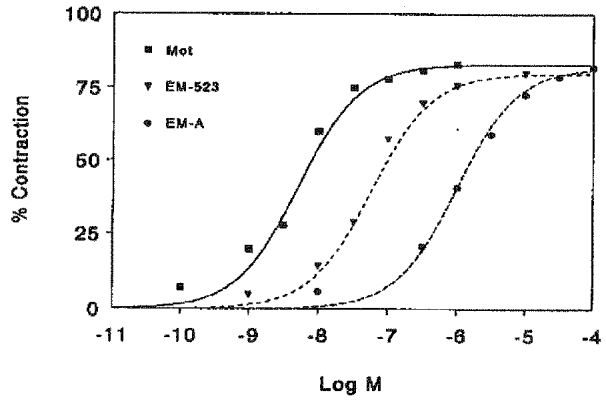

FIG. 5. Dose–response curves of the contractile activity exerted by [Nle^{13}-po]motilin, EM-523, and EM-A upon cat duodenal smooth muscle strips. The results were expressed relative to the maximum obtained with ACh (10^{-4} *M*).

the intrinsic activity of motilin (83 ± 3%), EM-523 (80 ± 5%), and EM-A (82 ± 5%), and strips maximally contracted by EM-A or EM-523 did not show an additional response with motilin.

Pharmacology

The maximal contractile response to [Nle^{13}-po]motilin (10^{-6} *M*) was not affected by 10^{-4} *M* atropine, although this dose of atropine abolished the response to ACh. Tetrodotoxin (1 μg/ml), which by itself induced a contraction (52% of the response towards ACh), was unable to block a [Nle^{13}-po]motilin-induced contraction. In contrast, verapamil at 10^{-4} *M* completely abolished the response towards [Nle^{13}-po]motilin, but not the response towards ACh, which was still 45% of the response obtained before the preincubation period (Fig. 6). In the presence of 10^{-6} *M* verapamil, the motilin response was 24% and the ACh response 83% of the response towards ACh under control conditions. After incubation for 10 min in a Ca^{2+}-free solution, the muscle strips showed no contractile activity when challenged with maximal concentrations of motilin (10^{-6} *M*), although ACh (10^{-4} *M*) was still able to induce 72% of the contractile activity obtained in normal conditions (data not shown). The response towards [Nle^{13}-po]motilin was also not affected by the ganglionic blocker, hexamethonium (10^{-4} *M*), and the 5-HT_3 antagonist, zacopride (10^{-4} *M*) (data not shown).

DISCUSSION

Our study indicates that the in vitro response of motilin is not exclusively limited to the observations made in rabbit and in man, but also extends to the cat. Motilin receptors are absent in the fundus, increase in number towards the duodenum, and then gradually decrease towards the ileum to completely disappear in the colon. This distribution of motilin receptors resembles the distribution found in man and in rabbit, except that in the rabbit motilin receptors are also present in the colon (7,22). In all three species, motilin receptor density is of the same order of magnitude.

In contrast, the affinity of motilin agonists (motilin, EM-A, EM-523, EM-A *N*-oxide) for the motilin receptor is clearly lower in cat than in rabbit, but somewhat higher than in man (5,7). However, in the three species the order of potency is the same: motilin > EM-523 > EM-A > EM-A *N*-oxide. In the cat, differences in affinity were also found between antrum and duodenum: in the stomach the affinity was higher than in the small intestine, and the difference seemed to depend upon the compound. Similar, although preliminary, observations have been made in the rabbit (9), indicating that there may be regional differences between motilin receptors. The data, however, are not conclusive and require further study.

The data obtained with the *N*-terminal motilin fragments are comparable with those found in the rabbit (6,19). Apparently the cat motilin receptor interacts with the same pharmacophore as in the rabbit. Detailed studies have shown that this pharmacophore involves the residues 1, 4, and 7 (25). Recently, we have isolated and sequenced cat motilin. The primary structure is identical to canine motilin, except that in position 12 lysine is replaced by arginine (10). Thus, for all motilins sequenced so far (pig, dog, man, cat, rabbit), the first six residues are identical, while number 7 is either tyrosine or histidine. This confirms the importance of the *N*-terminus.

There exists considerable difference between the mode of action of motilin and EM-A and its derivatives in different species. In vitro studies have shown that in rabbit and in man, but not in dog, rat, and guinea pig, motilin is able to interact directly with smooth muscle cells (1,28,29). In vivo studies show that in dog, motilin acts, at least in part, on nerves to release neurotransmitters: acetylcholine, opiates, or serotonin (11,12,16). It may also inhibit VIP release (13). However, Poitras et al. (26) reported that in dogs a smooth muscle receptor for motilin exists with a very low affinity, and Louie and Owyang (17) showed the presence of smooth muscle receptors for motilin in guinea pig. The fact that in the cat the in vitro contractile response towards motilin is only abolished by incubation of muscle strips in calcium-free media or with verapamil suggests that motilin exerts a direct effect upon smooth muscle cells. Studies in rabbit have shown that the response towards motilin is more dependent upon the influx of extracellular calcium than acetylcholine (20,21). A similar conclusion can be drawn from the results in the cat, as the response towards acetylcholine is only partially affected by verapamil and calcium-free media.

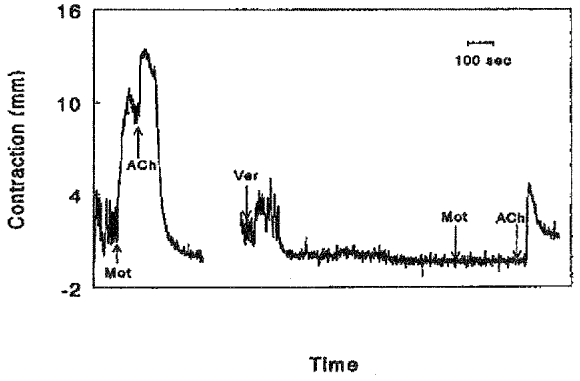

FIG. 6. Effect of pretreatment with verapamil (ver) on the contractile response of cat duodenal smooth muscle strips to [Nle^{13}-po]motilin. Left tracing shows the control response to [Nle^{13}-po]motilin (10^{-6} *M*) followed by a stimulation with ACh (10^{-4} *M*). Right tracing shows the same response of an adjacent strip first incubated for 10 min with verapamil (10^{-4} *M*), prior to challenge with [Nle^{13}-po]motilin (10^{-6} *M*) and ACh (10^{-4} *M*).

Erythromycin A and its derivatives displaced bound motilin and were able to induce contractions. The data are comparable with those found in rabbit, except that the potenties were lower. This corresponds to the lower affinity of the cat receptor for motilin. The similarity of action of motilin, EM-A, and its derivatives in different species adds further support to the motilin agonistic properties of these macrolide compounds.

There are no studies on the in vivo effect of motilin in the rabbit. In the cat, only the effect on the sphincter of Oddi has been studied (2). Consequently, the physiological role of motilin in these two species is unknown. In man and in dog, it has been proposed that motilin is involved in the induction of phase 3 activity of the migrating motor complex (MMC). However, this cannot be the physiological role of motilin in the cat, because the cat is thus far the only known mammalian species that does not exhibit MMCs in the fasting state. Giant migrating contractions (GMCs) seem to form the normal fasting motor pattern in the feline small intestine (27,31). In contrast, in man and in dog, GMCs occur infrequently and irregularly in the small intestine. But unlike humans and dogs, the GMCs in cat do not migrate uninterrupted over the entire length of the small intestine. The frequency of GMCs decreases linearly from the proximal duodenum to the proximal ileum, but then increases again to the distal ileum. Although the aborally decreasing incidence of GMCs correlates with the decrease of motilin receptor density, in vivo studies are needed to clarify a possible relation between motilin and GMCs.

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